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Factors reducing omalizumab response in severe asthma

B. Sposato^{a,*}, M. Scalese^b, M. Milanese^c, S. Masieri^d, C. Cavaliere^d, M. Latorre^e, N. Scichilone^f,
A. Matucci^g, A. Vultaggio^g, A. Ricci^h, A. Crestiⁱ, P. Santus^j, A. Perrella^a, P.L. Paggiaro^e

^a Pneumology Department, Misericordia Hospital, Grosseto, Italy^b Institute of Clinical Physiology, CNR, Pisa, Italy^c Pneumology Department, S. Corona Hospital, Pietra Ligure, Italy^d Otorhinolaryngology Clinic, Policlinico Umberto I, "Sapienza" University, Roma, Italy^e Cardio Thoracic and Vascular Department, Pathophysiology Unit, University of Pisa, Italy^f DIMPEFINU, Unit of Pneumology and Medicine, University of Palermo, Italy^g Immunology Unit, Department of Medicine and Geriatric, AOU Careggi, Florence, Italy^h Division of Pneumology, Department of Clinical and Molecular Medicine, Sapienza University of Rome, AOU Sant'Andrea, Rome, Italyⁱ Cardiology Department, Misericordia Hospital, Grosseto, Italy^j Department of Biomedical And Clinical Sciences (DIBIC), University of Milan, Respiratory Unit, "Luigi Sacco" University Hospital; ASST Fatebenefratelli-Sacco, Milan, Italy

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ABSTRACT

Background: Despite adding Omalizumab to conventional therapy, several severe asthmatics still show poor disease control. We investigated the factors that may affect a reduced Omalizumab response in a large population of severe asthmatics.

Methods: 340 patients were retrospectively evaluated. FEV₁%, FVC%, Asthma Control Test (ACT), fractional exhaled nitric oxide (FENO), possible step-downs/step-ups of concomitant therapies, exacerbations, disease control levels, ICS doses and SABA use, observed at the end of treatment, were considered as a response to Omalizumab.

Results: Age was an independent risk factor for a reduced response concerning FEV₁%, FVC%, ACT and for a lower asthma control. Obesity (vs normal weight) was a determinant condition for exacerbations (OR:3.114[1.509–6.424], $p = 0.002$), for a disease partial/no control (OR:2.665[1.064–6.680], $p = 0.036$), for excessive SABA use (OR:4.448[1.837–10.768], $p = 0.002$) and for an unchanged/increased level of concomitant asthma medications. Furthermore, obesity also reduced the response in FEV₁ ($\beta = -6.981, p = 0.04$), FVC ($\beta = -11.689, p = 0.014$) and ACT ($\beta = -2.585, p = 0.027$) and was associated with a higher FENO level ($\beta = 49.045, p = 0.040$). Having at least one comorbidity was a risk factor for exacerbations (OR:1.383[1.128–1.697], $p = 0.008$) and for an ACT < 20 (OR:2.410[1.071–3.690], $p = 0.008$). Specifically, chronic heart disease was associated with both a lower ACT and FVC% whereas gastroesophageal reflux with a partial/no asthma control. Nasal polyps were a predisposing factor leading both to exacerbations and to the use of higher inhaled corticosteroids doses. Moreover, smoking habits, pollen or dog/cat dander co-sensitizations may negatively influence Omalizumab response.

Conclusion: Age, obesity, comorbidities, smoking habits, nasal polyps, allergic poly-sensitization might reduce Omalizumab effectiveness independently to other asthma-influencing factors.

1. Introduction

Severe asthma is a disease phenotype requiring high-intensity treatment to obtain disease control [1]. However, low asthma control (i.e. a greater emergency department visits, hospitalizations and excessive short-acting β_2 -agonist and/or prednisolone use) characterizes a large part of subjects affected by "severe" asthma. In fact, despite using

high doses of inhaled corticosteroids (ICS), long acting bronchodilators and anti-leukotrienes, optimal asthma control may not be achieved in most patients affected by 'severe' asthma. In case of severe persistent uncontrolled asthma, caused by perennial allergens (mainly dust mite), guidelines recommend adding Omalizumab, a humanized recombinant DNA-derived monoclonal antibody [1]. It inhibits the interaction between IgE and the two main IgE receptors FcεRI and CD23/FcεRII

* Corresponding author at: U.O. Pneumologia, Azienda Ospedaliera "Misericordia", Via Senese 161; 58100 GROSSETO, Italy.

E-mail address: bruno.sposato@usldest.toscana.it (B. Sposato).

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FceRI, thus preventing mast cell and basophil activation and blocking IgE binding to CD23 on B-cells and antigen-presenting cells [2]. Practically, Omalizumab, specifically in real-life studies, has achieved a better asthma control by reducing daily corticosteroid dosages, exacerbations, hospitalizations and emergency department visits [3–7]. However, a high percentage (34%) of ‘severe’ asthmatics, although treated with Omalizumab, may show a poor disease control [5]. It is totally unclear which factors may negatively affect Omalizumab response. According to some authors [5,7], comorbidities (namely, obesity, gastro-oesophageal reflux disease, chronic rhinosinusitis, nasal polyps and mental disorders) and age are associated with the lack of asthma control and persistence of frequent disease exacerbations in severe asthmatics even though treated with Omalizumab. On the contrary, according to others [6], Omalizumab response in participants with comorbidities (rhinitis, obesity and cardiovascular diseases) was similar to the response in patients affected just by asthma. However, such results were obtained without adjusting for confounding factors like age, weight, therapy, blood eosinophils, age of asthma onset, aspirin intolerance, infections and others. The above said factors characterize several asthma phenotypes that may show a different response to treatment.

Therefore, aim of this study was to evaluate the possible factors that may influence Omalizumab effectiveness in a large population of severe asthmatics in a real-life setting, considering a large number of confounding clinical/biological factors that may cause a treatment interference.

2. Materials and methods

We retrospectively analyzed 340 severe asthmatics who had already been recruited for two of our previous studies [5,6,8]. All patients were severe allergic asthmatics poorly controlled despite a treatment with high doses of ICS plus long-acting bronchodilators, sometimes also associated with anti-leukotrienes, for which it was necessary to add Omalizumab, as recommended by steps 5 of asthma GINA guidelines [1]. All patients were under Omalizumab treatment for different periods of time (from 4 to 120 months). Lung function variables (FEV₁%, FVC%), Asthma Control Test (ACT), fractional exhaled nitric oxide (FENO), number of moderate/severe exacerbations, disease control, ICS doses, SABA use as rescue medication and possible variations in the use of other concomitant therapies (step-downs/step-ups), observed at the end of each patient's treatment period, were considered as responses to anti-IgE therapy. Asthma control levels were assessed by following GINA guidelines criteria [1]. Each patient's allergies had been established by prick tests to various aero-allergens. ACT ≥ 20 and FENO ≤ 25 ppb were considered normality cut-offs (good asthma control and low airway inflammation). Moderate/severe exacerbations requiring systemic corticosteroids for at least 3 days and/or hospitalizations were taken into account. Obesity Class I, II and III were defined by a BMI of 30–35, 35–40 and > 40 respectively. The daily dosage of beclomethasone dipropionate or equivalent dose for other corticosteroids used (fluticasone budesonide or others) was expressed as low (≤ 500 mg), medium (500–1000 mg) or high (≥ 1000 mg), according to GINA classification of ICS dose equivalence [1]. SABA use (number of times a week) during the 30 days before the end of each patient's treatment period with Omalizumab was also taken into account. As regards comorbidities, only those which had documented evidence were considered.

2.1. Statistical analysis

Our analysis was affected by using multivariate logistic and linear regression models. The tested variables (evaluated at the end of each patient's period of Omalizumab treatment) were the following: ACT < 20 vs > 20 ; FENO > 25 ppb vs < 25 ppb, no/partial asthma control vs good control, stable/increased therapy levels vs reduced

Table 1

Characteristics of 340 severe asthmatics treated with Omalizumab.

Age	53 [44–63]
Sex M/F	121/219 (35.6/64.4%)
Smokers	81 (24%)
Ex-smokers	23 (6.8%)
Pack/year	10 [5–20]
Smokers of < 10 pack/year	32 (9.5%)
Smokers of > 10 pack/year	29 (8.6%)
Age of asthma onset (yrs)	29 [15–40]
Family history with asthma	131 (45.6%)
House dust mite sensitization	276 (85.7%)
Pollen sensitizations	198 (63.5%)
Mould sensitizations	42 (13.5%)
Cat/dog dander sensitizations	90 (28.4%)
Mono-sensitized (to 1 allergen)	120 (37.3%)
Poly-sensitized (≥ 2 allergens)	202 (62.7%)
FEV ₁ % pre-Omalizumab ^a	74 [60–87]
FEV ₁ /FVC pre-Omalizumab ^a	71 [59–79.6]
Total serum IgE UI/ml	314.5 [167.5–553.5]
Blood eosinophils n/mm ^{3b}	270 [92–430]
FENO (ppb) ^c	25 [16–40]
N° of subjects with Eosinophils $> 3\%b$	113 (63.5%)
N° of subjects with rhinitis	224 (66.7%)
N° of subjects with sinusitis	117 (35.8%)
N° of subjects with nasal polyposis	78 (23.5%)
N° of subjects with hypertension	53 (22.5%)
N° of subjects with chronic heart disease	16 (6.8%)
N° of subjects with diabetes	8 (3.4%)
N° of subjects with osteoporosis	14 (5.9%)
N° of subjects with gastro-oesophageal reflux	116 (35.3%)
N° of subjects with OSAS	9 (3.9%)
N° of subjects with mental disorders	24 (8.5%)
BMI	26.48 [23.98–29.40]
N° of subjects with underweight	7 (2.1%)
N° of subjects with normal weight	110 (32.4%)
N° of subjects with overweight	146 (42.9%)
N° of subjects with obesity class I	51 (15%)
N° of subjects with obesity class II	21 (6.2%)
N° of subjects with obesity class III	5 (1.5%)
N° of subjects with 0 comorbidity	107 (31.8%)
N° of subjects with 1 $>$ comorbidity	233 (68.2%)
N° subjects with aspirin intolerance	62 (21.9%)
Monthly omalizumab dose (mg)	450 [300–600]
Months of omalizumab treatment	32 [17–50]
Patients in treatment with ICS	340 (100%)
Patients in treatment with LABA	300 (89%)
Patients in treatment with montelukast	195 (60.7%)
Patients in treatment with tiotropium	42 (13%)
Patients in treatment with theophylline	29 (10.9%)
Patients in treatment with oral corticosteroids	23 (8.4%)
Nasal steroids	114 (41.3%)

^a Evaluated on 125 patients where values were collected before starting Omalizumab

^b evaluated on 178 patients;

^c evaluated on 135 subjects

treatments, persistent high/unchanged dosages of ICS vs reduced ICS doses and SABA use $\geq$ once a week vs no SABA use. For the above said binary dependent variables (considered as the response of Omalizumab therapy), a stepwise multivariate logistic regression model was applied to test the relationship with several factors: sex, age, smoking habits, asthma familiarity, BMI (underweight, overweight, obesity class I [BMI = 30–35], II [BMI = 35–40], and III [BMI > 40]), various allergen sensitizations, IgE values, blood eosinophils, aspirin intolerance, infection recurrence, hypertension, diabetes, rhino-sinusitis, polyposis, chronic heart disease, osteoporosis, gastroesophageal reflux, COPD, mental disorders, age of asthma onset, Omalizumab treatment duration, daily doses of ICS, the use of Montelukast, oral corticosteroids and nasal steroids. For each continuous dependent variable (FEV₁%, FVC%, FENO, ACT), measured at the end of each patient's period of Omalizumab treatment, a stepwise multivariate linear regression model was applied to test the relationship with all the above listed covariates.

Table 2

Association between FEV₁, FVC, ACT, FENO, (considered as a response to Omalizumab treatment) obtained at the end of anti-IgE treatment, and numerous variables considered as confounding factors (sex, age, smoking habits, asthma familiarity, BMI (underweight, overweight, obesity class I [BMI = 25–30], II [BMI = 30–35], and III [BMI > 35]), various allergen sensitizations, IgE value, blood eosinophils, aspirin intolerance, infection recurrence, hypertension, diabetes, rhino-sinusitis, polyposis, chronic heart disease, osteoporosis, gastroesophageal reflux, COPD, mental disorders, age of asthma onset, Omalizumab treatment duration, daily doses of ICS Montelukast, oral corticosteroids and nasal steroids use). Only significant β coefficients obtained from linear regression models (stepwise forward procedure) are reported in table.

	FEV ₁ (%) (β)	FVC (%) (β)	ACT (β)	FENO (β)
Age	−0.398	−0.283	−0.046	
Underweight		−25.157		
Obesity class I	−6.981	−11.689	−1.840	
Obesity class II			−2.585	
Obesity class III				49.045
Chronic heart disease		−12.558		
Pollen co-sensitizations				17.508
Cat/dog dander co-sensitizations				−25.664

3. Results

Features of patients, observed before their being treated with Omalizumab, are reported in Table 1. At the end of Omalizumab treatment we observed that age was an important risk factor (independently of the other confounding variables considered) for reducing improvements in FEV₁%, FVC%, ACT and for worsening asthma control (Table 2; Figs. 2 and 3). Patients with obesity class I, compared to subjects with normal weight, highlighted a significant risk factor of having a greater number of exacerbations (OR: 3.114 [1.509–6.424], $p = 0.002$), a partial/no control of the disease (OR: 2.665 [1.064–6.680], $p = 0.036$) and an excessive SABA use (OR: 4.448 [1.837–10.768], $p = 0.002$), independently of various and several confounding variables considered (Figs. 1, 3 and 4). Obesity class I may also lead to a reduced increase in FEV₁ ($\beta = -6.981$, $p = 0.04$), FVC ($\beta = -11.689$, $p = 0.014$) and ACT ($\beta = -1.840$, $p = 0.021$) even after Omalizumab therapy (Table 2). Obesity class II was also a significant independent risk factor for a higher number of exacerbations and for an unchanged/increased level of therapy in time (OR: 3.194 [1.000–10.332], $p = 0.05$) (Figs. 1 and 6). Furthermore, obesity class II caused a reduced response in terms of ACT ($\beta = -2.585$, $p = 0.027$), independently of all the confounding factors considered by this study (Table 2). Obesity class III, compared to normal weight condition, was

associated with higher FENO level changes after treatment ($\beta = 49.045$, $p = 0.040$) (Table 2). Ex-smokers and smokers > 10 pack/year were prone to use more SABA than non-smoking patients, albeit treated with Omalizumab (Fig. 4). In addition, asthmatics with at least one comorbidity showed an increased risk factor for a high number of exacerbations (OR: 1.383 [1.128–1.697], $p = 0.008$) and for an ACT < 20 (OR: 2.410 [1.071–3.690], $p = 0.008$) (Figs. 1 and 2). In particular, asthmatics with chronic heart disease highlighted a significant predisposing factor for both a lower ACT (Fig. 2) and FVC% values (Table 2), when compared to subjects without this comorbidity and when the statistical analysis for all confounding variables was adjusted. The same happened for severe asthmatics with gastroesophageal reflux showing a higher risk for a partial/no control of the disease after Omalizumab (Fig. 3). Nasal polyps were also associated both with a higher number of exacerbations and a persistent treatment with ICS high/medium doses even after an anti-IgE therapy (Figs. 1 and 5). Subjects co-sensitized to pollen allergens (together with dust mite) showed FENO level changes ($\beta = 17.508$, $p = 0.029$) higher than the ones observed in patients non co-sensitized to pollens (Table 2). Furthermore, co-sensitization to dog/cat dander was a risk factor for a partial/no control of the disease (OR: 2.297 [1.209–4.364], $p = 0.011$) (Fig. 3), whereas, Omalizumab may favor an airway inflammation reduction (lower FENO levels) in asthmatics with this type of sensitization (Table 2).

On the contrary, asthmatics with asthma family history, rhinitis/sinusitis and a high level of total IgE may have a better response to Omalizumab (Figs. 4 and 5).

4. Discussion

According to our study, several factors may influence a reduced response to biological treatment with Omalizumab in a large population of severe asthmatics. In fact, age, obesity, chronic heart disease, gastroesophageal reflux, nasal polyps, dust mite co-sensitization with pollen and cat/dog allergens, were significantly associated with a reduced effectiveness in improving lung function (FEV₁%, FVC%), ACT (asthma control), FENO (airway inflammation) and disease control, in decreasing the number of exacerbations, SABA use as rescue medication and in favoring step-downs of other associated medications. Some of these results were also observed by previous studies [5–7]. However, they were not obtained by taking into account a large number of confounding factors. On the contrary, we observed that the above said factors act independently (without any interference of various asthma

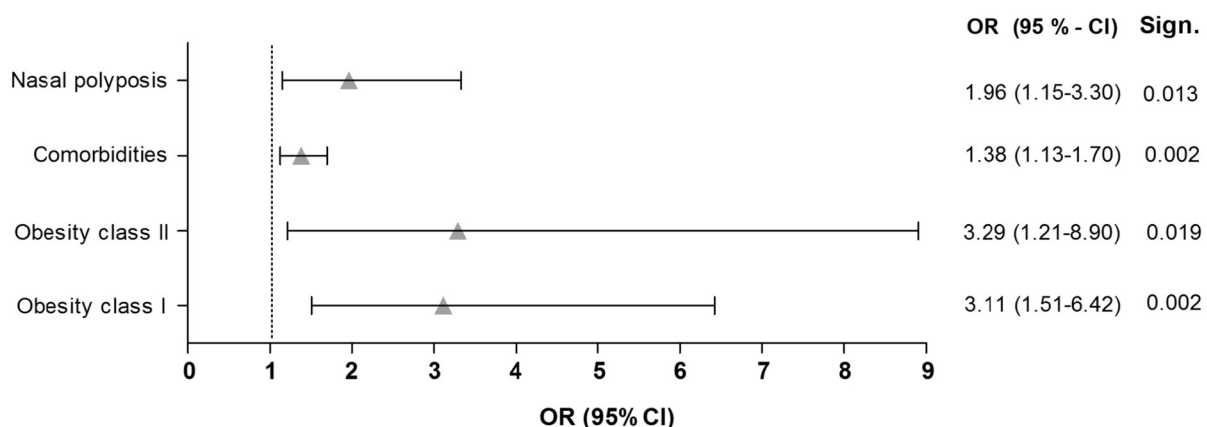


Fig. 1. Risk factors of having at least one exacerbation in a population of 340 severe asthmatics despite Omalizumab treatment.

Only significant ORs are reported in the figure. Subjects without any exacerbation were taken into account as reference. Odds ratios (OR) (▲) and 95% confidence intervals (CI) (–). The risk was calculated after a median of 32 [17–50] months of Omalizumab treatment.

Logistic regression model (stepwise forward procedure) was applied adjusting for sex, age, smoking habits, asthma familiarity, BMI (underweight, overweight, obesity class I [BMI = 30–35], II [BMI = 35–40], and III [BMI > 40]), various allergen sensitizations, IgE value, blood eosinophils, aspirin intolerance, infection recurrence, hypertension, diabetes, rhino-sinusitis, polyposis, chronic heart disease, osteoporosis, gastroesophageal reflux, COPD, mental disorders, age of asthma onset, Omalizumab treatment duration, daily doses of ICS Montelukast, oral corticosteroids and nasal steroids use.

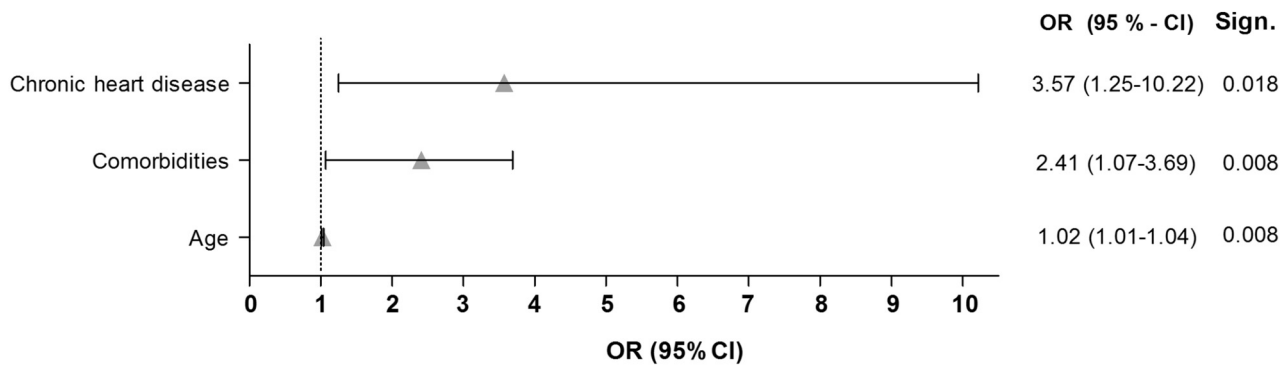


Fig. 2. Risk factors of having an ACT < 20 in 340 severe asthmatics despite Omalizumab treatment.

Only significant ORs are reported in the figure. Subjects without an ACT ≤ 20 were taken into account as reference. Odds ratios (OR) (▲) and 95%confidence intervals (CI) (–). The risk was calculated after a median of 32 [17–50] months of Omalizumab treatment.

Logistic regression model (stepwise forward procedure) was applied adjusting for sex, age, smoking habits, asthma familiarity, BMI (underweight, overweight, obesity class I [BMI = 30–35], II [BMI = 35–40], and III [BMI > 40]), various allergen sensitizations, IgE value, blood eosinophils, aspirin intolerance, infection recurrence, hypertension, diabetes, rhino-sinusitis, polyposis, chronic heart disease, osteoporosis, gastroesophageal reflux, COPD, mental disorders, age of asthma onset, Omalizumab treatment duration, daily doses of ICS Montelukast, oral corticosteroids and nasal steroids use.

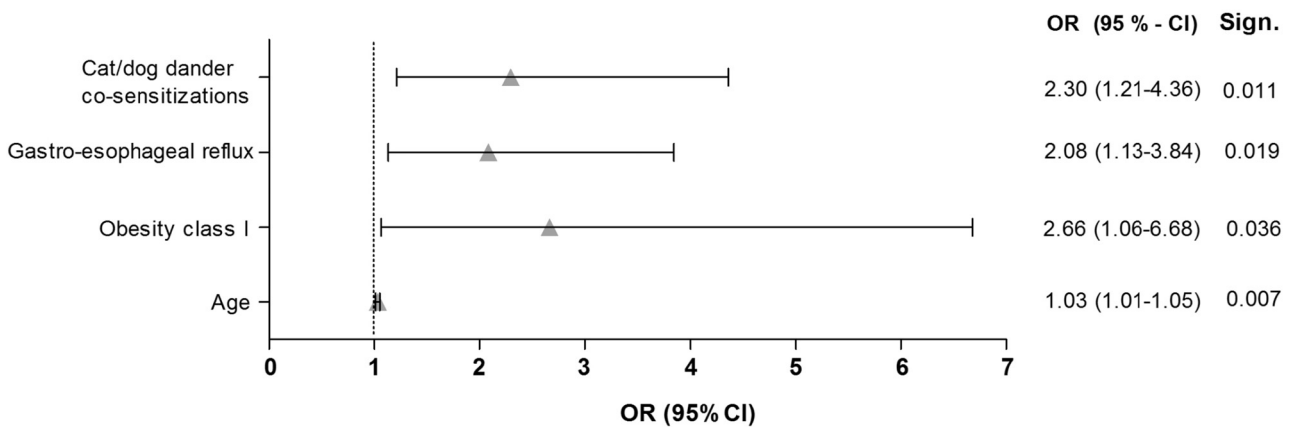


Fig. 3. Risk factors of having a partial/poor control of the disease in 340 severe asthmatics despite Omalizumab treatment.

Only significant ORs are reported in the figure. Subjects with a good asthma control were taken into account as reference. Asthma control levels were assessed by following GINA guidelines criteria. Odds ratios (OR) (▲) and 95%confidence intervals (CI) (–). The risk was calculated after a median of 32 [17–50] months of Omalizumab treatment.

Logistic regression model (stepwise forward procedure) was applied adjusting for sex, age, smoking habits, asthma familiarity, BMI (underweight, overweight, obesity class I [BMI = 30–35], II [BMI = 35–40], and III [BMI > 40]), various allergen sensitizations, IgE value, blood eosinophils, aspirin intolerance, infection recurrence, hypertension, diabetes, rhino-sinusitis, polyposis, chronic heart disease, osteoporosis, gastroesophageal reflux, COPD, mental disorders, age of asthma onset, Omalizumab treatment duration, daily doses of ICS Montelukast, oral corticosteroids and nasal steroids use.

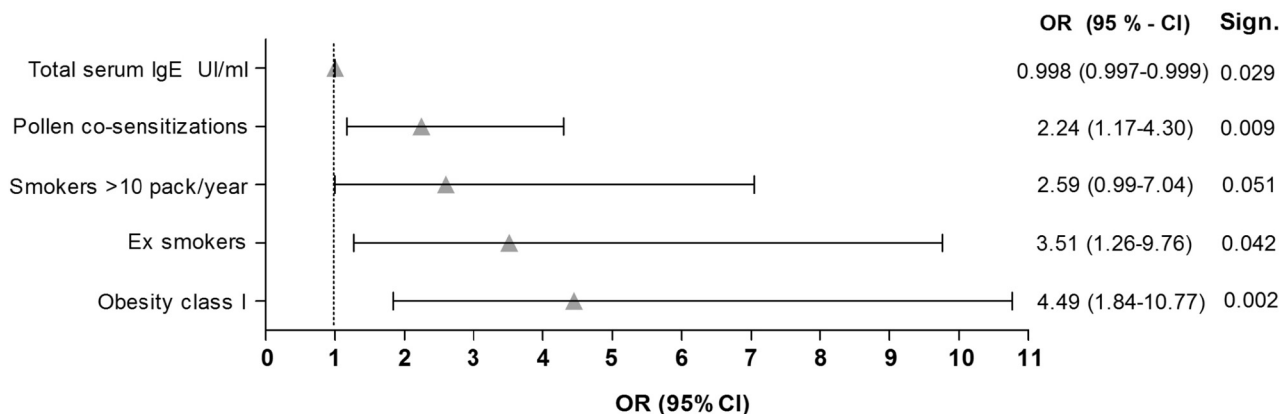


Fig. 4. Risk factors of using SABA at least once a week during the last month of therapy in 340 severe asthmatics despite an Omalizumab treatment.

Only significant ORs are reported in the figure. SABA use (number of times a week) during the month before the end of each patient's treatment period was taken into account. Subjects that not took SABA were considered as reference. Odds ratios (OR) (▲) and 95%confidence intervals (CI) (–). The risk was calculated after a median of 32 [17–50] months of Omalizumab treatment.

Logistic regression model (stepwise forward procedure) was applied adjusting for sex, age, smoking habits, asthma familiarity, BMI (underweight, overweight, obesity class I [BMI = 30–35], II [BMI = 35–40], and III [BMI > 40]), various allergen sensitizations, IgE value, blood eosinophils, aspirin intolerance, infection recurrence, hypertension, diabetes, rhino-sinusitis, polyposis, chronic heart disease, osteoporosis, gastroesophageal reflux, COPD, mental disorders, age of asthma onset, Omalizumab treatment duration, daily doses of ICS Montelukast, oral corticosteroids and nasal steroids use.

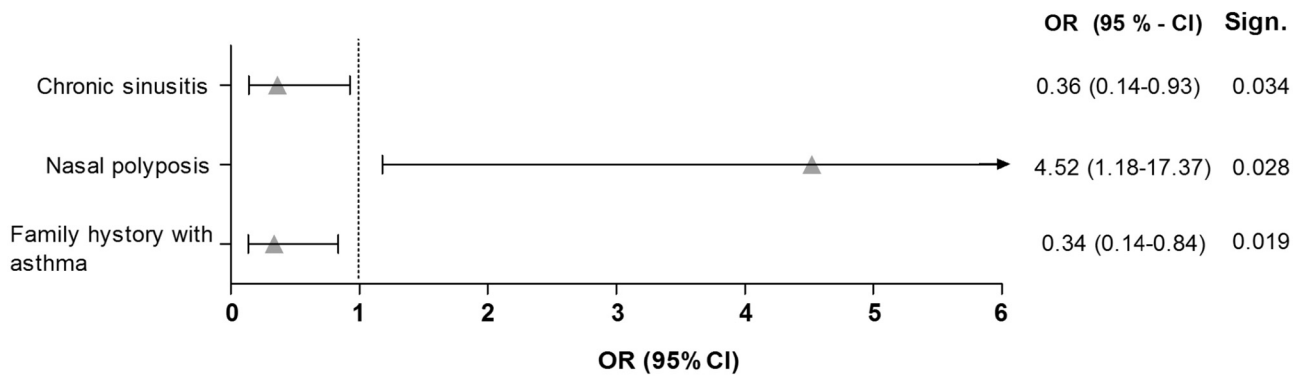


Fig. 5. Risk factors of continuing an ICS medium/high dose usage at the end of each patient's Omalizumab treatment period observed in 340 severe asthmatics.

Only significant ORs are reported in the figure. Subjects that took a low dose of ICS were considered as reference. Odds ratios (OR) (▲) and 95% confidence intervals (CI) (—). The risk was calculated after a median of 32 [17–50] months of Omalizumab treatment.

Logistic regression model (stepwise forward procedure) was applied adjusting for sex, age, smoking habits, asthma familiarity, BMI (underweight, overweight, obesity class I [BMI = 30–35], II [BMI = 35–40], and III [BMI > 40]), various allergen sensitizations, IgE value, blood eosinophils, aspirin intolerance, infection recurrence, hypertension, diabetes, rhino-sinusitis, polyposis, chronic heart disease, osteoporosis, gastroesophageal reflux, COPD, mental disorders, age of asthma onset, Omalizumab treatment duration, daily doses of ICS Montelukast, oral corticosteroids and nasal steroids use.

influencing variables) on determining a reduced response and therefore a worse asthma control in severe disease phenotypes despite a high treatment level even with Omalizumab. Already in the past, randomized clinical trials (RCT) testing effectiveness of Omalizumab in severe asthma had shown that there was a fair number of patients who were poorly responsive to this treatment [8–12]. However, the cause of this poor response to therapy has never been investigated in these studies. Probably, this poor response to treatment, seen in RCTs, concerned just the elderly, obese asthmatics, smokers and subjects with comorbidities as showed by our study. Furthermore, obesity, advanced age, comorbidities and smoking exposure may be potentially responsible/associated for/to asthma-like symptoms and may lead to a false asthma diagnosis, i.e., patients with symptoms suggestive of asthma may actually have different diseases showing similar symptoms [13]. In our study, however, all patients were severe asthmatics with a certain severe asthma diagnosis. More restrictive criteria are necessary

for an Omalizumab prescription in Italy. Each center was strictly adherent to such criteria. Therefore, obesity, advanced age, comorbidities, smoking exposure and other factors are, according to our study, overlapping conditions/diseases influencing asthma negatively and consequently its treatment.

As already said, age is a risk factor for a reduced ACT rate and therefore for a lower asthma control after Omalizumab, similarly to what had already been observed in a previous study [7]. In fact, according to such study, a lower level of ACT and a greater number of exacerbations were obtained after Omalizumab in elderly subjects compared to younger subjects. The different responsiveness to Omalizumab between younger and older subjects was supposed to be caused by comorbidities, obesity and later asthma onset which were common in the elderly. Instead, we found that just age was an independent factor negatively influencing Omalizumab effectiveness without any interference of the above mentioned confounding variables. Furthermore,

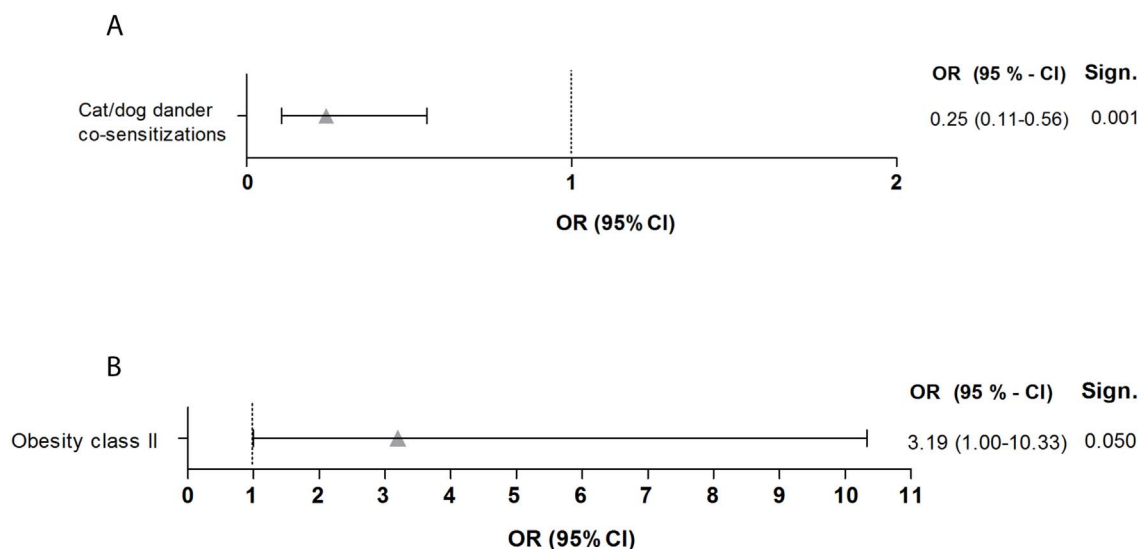


Fig. 6. Risk factors of showing a FENO > 25 (A) or an unchanged/stepped up of other concomitant asthma medications (more than Omalizumab) (B) at the end of each patient's Omalizumab treatment period observed in 340 severe asthmatics.

Only significant ORs are reported in the figure. Subjects with FENO < 25 or that showed a step down of other concomitant medications (in addition to Omalizumab) at the end of each patient's Omalizumab treatment period were considered as reference. Odds ratios (OR) (▲) and 95% confidence intervals (CI) (—). The risk was calculated after a median of 32 [17–50] months of Omalizumab treatment.

Logistic regression model (stepwise forward procedure) was applied adjusting for sex, age, smoking habits, asthma familiarity, BMI (underweight, overweight, obesity class I [BMI = 30–35], II [BMI = 35–40], and III [BMI > 40]), various allergen sensitizations, IgE value, blood eosinophils, aspirin intolerance, infection recurrence, hypertension, diabetes, rhino-sinusitis, polyposis, chronic heart disease, osteoporosis, gastroesophageal reflux, COPD, mental disorders, age of asthma onset, Omalizumab treatment duration, daily doses of ICS Montelukast, oral corticosteroids and nasal steroids use.

our analysis showed also a reduced response in terms of lung function with increasing age. In fact, the latter may lead to the development of a progressive airway remodeling in time [14,15]. Elderly asthmatics had a significantly greater airway wall thickening and air trapping than younger patients [16]. Therefore, lung function decline may influence not only the response to Omalizumab but also to all other asthma treatments. A progressively increasing neutrophilic airway inflammation, occurring with age [17], may be responsible for an accelerated lung function decline and for a reduced treatment effectiveness [18]. In fact, neutrophilic asthma was associated with a poor response to ICS treatment [19–21] and probably also with Omalizumab, as opposed to what happens to eosinophilic asthma. Age may be also responsible for the development of immune-senescence inducing immune system function decline. This age-related process leads to a progressive impaired mucociliary clearance, to changes in airway neutrophil, eosinophil, and mast cell numbers and to an altered antigen presentation and decreased specific antibody responses [22]. Furthermore, immune-senescence, and its concomitant chronic low grade systemic “inflammaging”, may contribute to the worsening of pulmonary disease in older individuals [23,24]. Therefore, it may favor a neutrophilic inflammation thus leading to a more severe disease, lung function decline and less effective treatments in elderly people [20] and consequently to a reduced asthma control even in Omalizumab treated patients.

In our study, obesity (compared to normal weight condition), independently of other confounding factors, was a condition that may lead to a reduced effectiveness to Omalizumab treatment (higher number of exacerbations, a reduced ACT increase and a lower asthma control). A significant relationship between obesity and asthma had already been assessed [25,26]. Undeniably, the proportion of obese subjects increases with asthma severity, reaching its peak in the highest asthma severity step [27]. Furthermore, several studies have shown an inverse relationship between BMI categories and reduction in asthma control, as a response to all controller therapies (ICS, antileukotrienes and ICS in combination with long-acting β_2 agonists) [28–30]. There may be several reasons for such reduced obesity-induced responsiveness to treatment. Firstly, overweight/obese status, with an increased subcutaneous and visceral abdominal fat mass, may be a risk factor for a higher airway hyperresponsiveness and airway narrowing (by means of a lung volume reduction) [31–36] leading to a greater asthma severity which is more difficult to be treated. Secondly, obesity may also lead to a state of low-grade systemic inflammation (increased leptin, TNF- α , IL-6, TGF- β 1, adiponectin and C-reactive protein) that may cause a worsening of asthma airway inflammation [25,32,36]. In fact, we found that the change in FENO level (a marker of airway inflammation) was higher in subjects with class III obesity when compared to severe asthmatics with normal weight, thus confirming a greater airway inflammation in obese subjects that can lead to a greater severity of the disease and thus to a reduced response to treatment. A higher risk of having a reduced FEV₁ increase after Omalizumab was also observed in obese subjects. Obesity (which occurs with age), by means of a higher airway inflammation, may favor an airway remodeling and therefore a lung function decline probably reducing the response to Omalizumab and other treatments. Actually, some authors have found that CRP, Leptin and IL-6 were higher in obese asthmatics and that this cytokine was negatively correlated with FEV₁ and FVC [25]. In addition, obese asthmatics showed more neutrophils in sputum and blood than non-obese patients [37]. This was related with a reduced improvement in lung function after a two-week treatment with corticosteroids [37], confirming that neutrophilic obesity-induced airway inflammation is related to a lower responsiveness to anti-inflammatory therapy. In fact, non-eosinophilic asthma sub-phenotypes, like obesity-induced asthma, are associated with corticosteroid insensitivity as well as bronchial hyper-reactivity and airway remodeling [21,38]. This is confirmed by some studies, where obese asthmatics showed an accelerated decline in lung function when compared to normal weight subjects [39,40]. Furthermore, some authors have

ascertained that airway smooth muscle cell hyperplasia is more significant in asthmatics than in healthy subjects. This may lead to increased airway stiffness and above all to a progressive airway narrowing over time [41]. Besides, mechanical airway wall factors (smooth muscle cell hyperplasia with increased airway stiffness) may have a crucial role in determining a lower response to treatment and thus also to Omalizumab in obese asthmatics. Furthermore, obese asthmatics are more likely to have obesity-related comorbidities such as obstructive sleep apnea and gastroesophageal disease that can complicate asthma and reduce treatment responses [42,43]. Indeed, we found that comorbidities were independently associated with an increased risk of showing a higher number of asthma exacerbations and a lower ACT level after Omalizumab treatment. We know that comorbidities are associated with uncontrolled asthma [44–46]; however, there is no data in literature about the way comorbidities may worsen the severity of the disease and how they may reduce treatment effectiveness. Particularly, we found that cardiovascular diseases were a strong risk factor for a more restrictive spirometry pattern (reduced FVC%), surely due to an association with chronic heart failure which may determine a higher risk of having a low ACT value. In addition, we found that also GER may be a risk factor for a worse asthma control, despite Omalizumab treatment. It seems that up to 70% of patients with uncontrolled asthma are affected by GER [47] and that therapy with Omeprazole improves both nocturnal and daytime asthma symptoms, pulmonary function and decreases requirement of asthma medications in these patients [47]. We also found that nasal polyps may reduce Omalizumab effectiveness. In fact, nasal polyps were also associated to a higher risk of having a greater number of exacerbations and to the need of using high doses of ICS despite Omalizumab treatment. Nasal polyps and asthma are strongly associated, and patients suffering from both diseases are often difficult to be treated [48]. Furthermore, nasal polyps may induce a greater worsening of airway inflammation and consequently of asthma [49,50], so influencing response to therapy.

Therefore, comorbidities can affect asthma severity and treatments effectiveness. For this reason they should be taken into account when managing lung diseases and should be treated together.

According to a recent article [51], Omalizumab treatment leads to a marked improvement of asthma control and a better quality of life in smokers, although lung function (FEV₁, FVC or FEV₁/FVC ratio) remains unchanged. The increased risk of using SABA in asthmatics with a smoking history, observed by our study, is probably due to a greater smoking-induced bronchial hyperresponsiveness [52] and therefore to a marked airways narrowing.

Pollen co-sensitizations with dust mite observed to prick tests resulted to be a risk factor for a greater airway inflammation (measured by FENO) and for a higher SABA use. Undeniably, symptoms severity was higher in polysensitized patients [53]. *Parietaria*-allergy was especially responsible for the most severe symptoms [53], thus demonstrating that a poly-sensitization including pollens can worsen asthma and probably reduce Omalizumab effectiveness. In addition, co-sensitization to dog/cat dander can negatively influence disease control, whereas, Omalizumab may induce a reduction of airway inflammation in subjects with this type of sensitization. Many studies have found a positive correlation between animal allergen exposure and incidence of allergies, although this association has not been always confirmed. On the contrary, some studies have shown that high exposure to animal allergens can have a protective effect against IgE sensitization and allergies [54].

It is Interesting as our study highlighted that asthma family history, rhinitis/sinusitis and a high level of total IgE may be predictive of a better response to Omalizumab treatment. This suggests the existence of a specific phenotype of patients who might respond to such treatment more adequately.

4.1. Strengths and limitations

The novelty of this study is that even in the severe asthma phenotype there are several factors that may affect the therapy response even when using biological treatment. Moreover, we also ascertained that the factors influencing therapy response are all independent of one another, suggesting a possible negative effect of the same factors responsible for a lower effectiveness. We also hypothesize that age, obesity, comorbidities and other variables may also be a marker indicating a possible low response to treatment in all asthma phenotype, considering that a large number of the confounding factors taken into account are typical of several asthma phenotypes. In this case, age, obesity, comorbidities specific pattern of sensitizations and IgE levels may even be specific characteristics of different severe asthma endotypes. Perhaps, we should think of increasing drug doses or the therapy level and the multi-disciplinary treatment of all asthmatics with the above said factors that may influence treatment.

The retrospective analysis of data may be regarded as a drawback of this study. However, the large number of recruited patients has reduced possible bias. Another negative aspect may be the lack of data on neutrophilic airway inflammation of our patients which may be an important factor that could have contributed to the lower response to therapy, probably just induced by age, obesity, smoking, etc.

5. Conclusions

In conclusion, age, obesity, comorbidities, smoking habits, nasal polyposis and allergic poly-sensitization may reduce the effectiveness of Omalizumab treatment independently of all possible different confounding factors that may interfere with asthma severity and therefore with the response to treatment.

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